

## PATENT ABSTRACTS OF JAPAN

(11)Publication number : 11-033407

(43)Date of publication of application : 09.02.1999

---

(51)Int.Cl.

B01J 31/22

C07B 53/00

C07C227/12

C07C229/34

C07C327/22

// C07B 61/00

C07M 7:00

---

(21)Application number : 09-197589

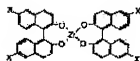
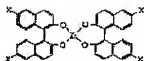
(71)Applicant : RES DEV CORP OF JAPAN

(22)Date of filing : 23.07.1997

(72)Inventor : KOBAYASHI OSAMU

---

(54) ASYMMETRIC ZIRCONIUM CATALYST



## (57)Abstract:

**PROBLEM TO BE SOLVED:** To carry out asymmetric org. synthesis with high reactivity and selectivity by preparing an asymmetric zirconium catalyst having such a structure that zirconium (IV) is used as the active center atom of the catalyst and that two molecules are bonded through optically active binaphthyl groups and oxygen atoms to the center zirconium.

**SOLUTION:** This asymmetric zirconium catalyst has such a structure that zirconium (IV) is used as the active center atom of the catalyst and that two molecules are bonded through optically active binaphthyl groups and oxygen atoms to the zirconium. The optically active binaphthyl groups are derived from optically active binaphthols, and hydrogen atoms bonded to the naphthalene ring may be replaced by any of various kinds of org. groups as far as the org. groups do not inhibit the

function as an asymmetric catalyst. The optically active binaphthyl groups are R-1,1'-bi-2-naphthyl groups, etc., and basically have the structure expressed by formulae I, II. In the formulae, X represents hydrogen or a halogen atom.

---

CLAIMS

---

## [Claim(s)]

[Claim 1] A dissymmetry zirconium catalyst having the structure which used JIRUKONIMU (IV) as an active center atom of a catalyst, and said zirconium combined via optical activity dyad binaphthyl group and oxygen atom.

[Claim 2] A dissymmetry zirconium catalyst of claim 1 by which at least one of the hydrogen atoms of an optical activity binaphthyl group is replaced by halogen atom, nitro group, cyano group, alkyl group, or an alkoxy group.

[Claim 3] A dissymmetry zirconium catalyst of claim 1 or 2 based on structure expressed with following formula (I) where optical activity binaphthyl groups are 1 of R-object or S-object, and 1'-\*\*\*- 2-naphthyl group or 6, and 6'-dihalogeno 1, and a 1'-\*\*\*- 2-naphthyl group.

## [Formula 1]

[Claim 4] A dissymmetry zirconium catalyst which an imidazole derivative has configurated in a zirconium atom of one dissymmetry zirconium catalyst of claims 1 thru/or 3.

[Claim 5] A dissymmetry zirconium catalyst of claim 4 whose imidazole derivative is at least one sort chosen from a group of N-alkyl imidazole and alkylation imidazole.

[Claim 6] A manufacturing method of a dissymmetry zirconium catalyst making a zirconium (IV) tetraalkoxide which is a manufacturing method of one dissymmetry zirconium catalyst of claims 1 thru/or 5, and is expressed with following formula (II), and optical activity binaphthols react.

## [Formula 2]

[Claim 7] A manufacturing method of a dissymmetry zirconium catalyst of claim 6 whose zirconium (IV) tetraalkoxide is zirconium (IV)t-butoxide.

[Claim 8] A manufacturing method of a dissymmetry zirconium catalyst of claim 7 to which zirconium (IV)t-butoxide and optical activity binaphthol are made to react in a methylene chloride under existence of an imidazole derivative.

[Claim 9] A manufacturing method of an optically active compound which is a manufacturing method of an optically active compound by an addition reaction of imine and a nucleophile, and is characterized by making it react under existence of one dissymmetry zirconium catalyst of claims 1 thru/or 5.

[Claim 10] A manufacturing method of an optically active compound of claim 9 which carries out the addition reaction of the imine prepared from 2-aminophenols and a

carbonyl compound to a nucleophile as imine.

[Claim 11]A manufacturing method of an optically active compound of claim 9 or 10 whose nucleophile is silyl enol ether.

[Claim 12]A manufacturing method of an optically active compound which is a manufacturing method of an optically active compound by an addition reaction of imine and a nucleophile, and is characterized by using an imidazole derivative as an additive agent and making it react under existence of one dissymmetry zirconium catalyst of claims 1 thru/or 3 in addition to inside of the system of reaction.

[Claim 13]A manufacturing method of one optically active compound of claims 9 thru/or 12 whose optically active compounds are beta-aminoester.

---

---

DETAILED DESCRIPTION

---

## [Detailed Description of the Invention]

[0001]

[Field of the Invention]The invention of this application relates to the dissymmetry zirconium catalyst which has the zirconium embellished by optical activity binaphthol in an active center, its manufacturing method, and the manufacturing method of the optically active compound using it.

[0002]

[Description of the Prior Art]Although the dissymmetry imino aldol reaction is known as one of the important manufacturing methods of a nitrogen-containing compound [ optical activity / before ], They an optical activity reactional substrate. JIASUTEREO to be used -- an alternative reaction (Angew.) Chem., Int. Ed. Engl., 34 volumes, 2861 pages, 1995;J. Org. Chem., 51 volumes, 6902 pages, 1993;J. Am. Chem. Soc., 112 volumes, 8215 pages, 1990, others, Or the asymmetric source more than the amount of stoichiometries. the needing method (Angew. Chem.) It was restricted in Int. Ed. Engl., 35 volumes, 981 pages, 1996;Liebigs Ann. Chem., 233 pages, 1992;J. Am. Chem. Soc., 116 volumes, 10520 pages, and 1994.

[0003]Also generally acquisition and preparation are difficult for optical activity reactional substrate and asymmetric source, or it is expensive in many cases. For this reason, development of the catalytic asymmetric synthesis reaction which can compound a lot of optically active compounds from a small amount of asymmetric sources was desired strongly. in the field of synthetic organic chemistry -- high yield -- high -- the alternative reaction is called for, the synthetic reaction with little waste fluid and waste is further called for from viewpoints of an environmental problem etc. in recent years, and it is thought that efficient catalytic reaction contributes to streamlining of experiment waste greatly.

[0004]Although realization of an alternative method is just going to be expected with the high yield which uses a catalyst also from such a viewpoint about the dissymmetry imino aldol reaction as an asymmetric synthesis reaction of an optical activity nitrogen-containing compound, However, the actual condition is that the catalytic dissymmetry imino aldol reaction is not known until now. Then, the invention of this application makes it SUBJECT to provide the new asymmetric catalyst which can conquer the conventional technical limit and can perform catalytically dissymmetry organic synthesis, such as a dissymmetry imino aldol reaction, with high reactivity and

selectivity, and its manufacturing method. This invention makes it SUBJECT to provide manufacturing methods, such as optical activity beta-aminoester which used said asymmetric catalyst.

[0005]

[Means for Solving the Problem]Namely, first an invention of this application as what solves aforementioned SUBJECT to the 1st. JIRUKONIMU (IV) is used as an active center atom of a catalyst, and a dissymmetry zirconium catalyst (claim 1) having the structure which said zirconium combined via optical activity dyad binaphthyl group and oxygen atom is provided.

[0006]At least one of the hydrogen atoms of an optical activity binaphthyl group as that mode about this catalyst And a halogen atom, A dissymmetry zirconium catalyst (claim 2) replaced by nitro group, cyano group, alkyl group, or an alkoxy group is begun, A dissymmetry zirconium catalyst based on structure expressed with following formula (I) where optical activity binaphthyl groups are 1 of R-object or S-object, and 1'-\*\*\*-2-naphthyl group or 6, and 6'-dihalogeno 1, and a 1'-\*\*\*-2-naphthyl group (claim 3), [0007]

[Formula 3]

[0008]The dissymmetry zirconium catalyst (claim 4) which the imidazole derivative has configured in the zirconium atom, and an imidazole derivative provide the dissymmetry zirconium catalyst (claim 5) etc. which are at least one sort chosen from the group of N-alkyl imidazole and alkylation imidazole. The invention of this application is a manufacturing method of the above dissymmetry zirconium catalyst, and provides the 2nd with the manufacturing method (claim 6) of the dissymmetry zirconium catalyst making the zirconium (IV) tetraalkoxide expressed with following formula (II), and optical activity binaphthols react.

[0009]

[Formula 4]

[0010]As the mode, a zirconium (IV) tetraalkoxide, The manufacturing method (claim 7) of the dissymmetry zirconium catalyst which is zirconium (IV)t-butoxide, The manufacturing method (claim 8) of the dissymmetry zirconium catalyst to which zirconium (IV)t-butoxide and optical activity binaphthol are made to react in a methylene chloride is also provided under existence of an imidazole derivative.

[0011]An invention of this application is a manufacturing method of an optically active compound by an addition reaction of imine and a nucleophile as the 3rd, A manufacturing method (claim 9) of an optically active compound making it react under existence of the aforementioned dissymmetry zirconium catalyst, A manufacturing

method of an optically active compound which carries out the addition reaction of the imine prepared from 2-aminophenols and various carbonyl compounds as imine as the mode to a nucleophile (claim 10), In a manufacturing method (claim 11) of an optically active compound whose nucleophile is silyl enol ether, and an addition reaction of imine and a nucleophile, A manufacturing method (claim 12) of an optically active compound made to react by using an imidazole derivative as an additive agent under existence of said dissymmetry zirconium catalyst in addition to inside of the system of reaction and an optically active compound also provide one manufacturing method of more than which are beta-aminoester (claim 13).

[0012]

[Embodiment of the Invention] Hereafter, the embodiment of the invention of this application is described. using 1 zirconium (IV) as the active center atom of a catalyst as that basic structure about the dissymmetry zirconium catalyst of this invention as aforementioned -- 2 -- it is making for this zirconium to have joined together via optical activity dyad binaphthyl group and oxygen atom into that requirement. Although a binaphthyl group [ optical activity / in this case ] is typically led from optical activity binaphthol, as long as it does not check the function as an asymmetric catalyst, the hydrogen atom combined with a ring may be replaced by the naphthalene ring by various kinds of organic groups. For example, that by which at least one of the hydrogen atoms was replaced by a halogen atom, a nitro group, a cyano group, an alkyl group, alkoxy group, etc. is mentioned as an example. Especially, the binaphthyl group which the halogen atom replaced is shown. 1 of R-object [ which is expressed as formula (I) of further the above ] or S-object and 1'-\*\* 2-naphthyl group or 6, and 6'-dihalogeno 1 and a 1'-\*\*\* 2-naphthyl group are shown as one of the suitable things.

[0013] About such a dissymmetry zirconium catalyst, an organic compound may configurate further. As such an organic compound, a nitrogen-containing organic compound is illustrated as a desirable thing. Especially, nitrogen-containing heterocyclic compounds and diamine compounds, such as imidazole derivatives, Indore, pyrimidines, and pyrazines, are mentioned. More specifically, alkylation imidazole, such as N-alkyl imidazole, such as N-methylimidazole and N-ethylimidazole, and 1,2-dimethylimidazole, is illustrated.

[0014] In order to use the above dissymmetry zirconium catalyst, the dissymmetry zirconium catalyst acquired by making the zirconium (IV) tetraalkoxide typically expressed with said formula (II) and optical activity binaphthols react is isolated from the catalyst constructional system, Or it can be used for a desired organic synthesis reaction, without isolating. When using a zirconium (IV) tetraalkoxide as a raw

material as mentioned above, about an alkoxy group, it may be [ constructional system / catalyst ] various kinds of things, but t-butoxy group is illustrated as a desirable thing also in a lower alkoxy group. As a reactional solvent, although halogenated hydrocarbon, amide, and nitril are used, it is preferred to choose from what is further used also as that solvent, without checking this synthetic reaction, in using for an organic synthesis reaction, without isolating a catalyst.

[0015]What is necessary is just to choose suitably according to the temperature and time of a catalyst synthetic reaction, the kind of raw material, etc., and, generally it may be about -10-40 °C about temperature. It may add to the system of reaction of catalyst composition, or the organic compound which the aforementioned imidazole derivatives etc. can configurate may be added to the organic synthesis system of reaction using a catalyst.

[0016]The preparation rate of the binaphthol of optical activity, t-butoxide as a zirconium (IV) raw material compound, etc. should just make 2:1 a rule of thumb as a mole ratio fundamentally. About organic compounds, such as imidazole derivatives, molar quantity can be made into a rule of thumb one to 3 times to a zirconium (IV) raw material compound. The dissymmetry zirconium catalyst as more than [ of this invention ] can be used for various kinds of dissymmetry organic synthesis reactions. Especially, using for manufacture of the optically active compound by the addition reaction of imine and a nucleophile as an invention of this application is proposed.

[0017]In this reaction, as for imine, what is obtained by the reaction of an amine compound and a carbonyl compound may be arbitrary, for example, the imine adjusted from 2-aminophenols and a carbonyl compound useful as an organic synthesis intermediate, an intermediate of medicine or agricultural chemicals, etc. is illustrated. Although it may be various kinds of things also as one nucleophile, silyl enol ether will be illustrated in the addition reaction of 2-aminophenols.

[0018]although the amount of the dissymmetry zirconium catalyst used to these organic synthesis systems of reaction is different also according to the system of reaction -- general -- about 0.1-50 mol % -- let about 1-30 mol % be a rule of thumb comparatively more preferably. It will decide on reaction temperature, time, etc. suitably.

[0019]

[Example]Below, the example of this invention is described. Of course, this invention is not limited by the following examples.

Example 1 tetra t-butoxyzirconium ( $\text{Zr}(\text{O}-t\text{-Bu})_4$ , 4mmol) is made suspended to a methylene chloride (25 ml), The methylene chloride (10 ml) solution of



6,6'-dibromo-1,1'-\*\*-. 2-naphthol (8mmol) and the methylene chloride (5 ml) solution of N-methylimidazole (8mmol) were added to this thing under the room temperature, and it stirred for 1 hour. Reduced pressure drying of the solvent was carried out after decompression distilling off, and the dissymmetry zirconium catalyst (catalyst 1) with the structure shown in above formula (I) (X=Br) was acquired (yield of 4.56g).

[0020]The NMR spectrum of this catalyst 1 was shown in drawing 1. Subsequently, this catalyst 1 (10·mol%) was dissolved in the methylene chloride (0.25 ml), and it cooled at -45 \*\*. The methylene chloride (0.5 ml) solution of imine (0.8mmol) adjusted from 1-naphthaldehyde and 2-aminophenol according to the following reaction formula, Then, after adding the methylene chloride (0.025 ml) solution of the 1-methoxy-2-methyl-1-trimethylsiloxy propene (0.96mmol) and stirring for 10 hours, the sodium bicarbonate solution of saturation was added and the reaction was suspended. The methylene chloride extracted and decompression distilling off of the solvent was carried out after desiccation with anhydrous sodium sulfate. Tetrahydrofuran 1N chloride (10:1) was added to the obtained rough product under ice-cooling, and it stirred for 30 minutes. Silica gel column chromatography refined the solvent after decompression distilling off, and the compound as a beta-aminoester derivative was obtained quantitatively. HPLC using an optical activity column determined the optical purity (92%ee) of the obtained compound.

[0021]The NMR spectrum of this compound was shown in drawing 2, and the IR spectrum was shown in drawing 3.

[0022]

[Formula 5]

[0023]Replaced with the 6,6'-dibromo-1 in example 2 Example 1, and 1'-\*\*-. 2-naphthol, it was made to react similarly using 1 and 1'-\*\*-. 2-naphthol, and the dissymmetry zirconium catalyst (catalyst 2) was acquired. The synthetic reaction was carried out like Example 1 using this catalyst 2, and the same compound was obtained by 80% of yield, and an optical purity 70ee ratio.

In example 3 Example 1, when the catalyst (catalyst 3) was prepared and the synthetic reaction was performed like Example 1 using this catalyst 3, without using N-methylimidazole, 54% of optical purity obtained the same compound by ee quantitatively.

Example 4 tetra-*t*-butoxyzirconium (Zr(O-*t*-Bu) <sub>4</sub>, 0.04mmol) is made suspended to a methylene chloride (0.25 ml), Then, the methylene chloride (0.5 ml) solution of 6,6'-dibromo-1,1'-\*\*-. 2-naphthol (0.088mmol) and the methylene chloride (0.25 ml) solution of N-methylimidazole (0.048mmol) were added at the room temperature. The

synthetic reaction was carried out like Example 1, without having cooled at -45 \*\*, having adjusted the catalyst after 1-hour stirring, and isolating this catalyst. The same compound was quantitatively obtained as a thing of ee optical purity 95%. In example 5 Example 4, N-methylimidazole was replaced with 1,2-dimethylimidazole and the synthetic reaction was similarly carried out at the temperature of -15 \*\*.The same compound was quantitatively obtained as a thing of ee optical purity 91%.

In example 6 Example 4, the synthetic reaction was similarly carried out for the amount of the catalyst used as 1/5 quantity. The same compound was obtained as a thing of ee optical purity 86% with yield 75%.

Various imine and the reaction of the silyleno rate were performed in accordance with the same method as example 7 Example 4. The result was shown in Table 1.

[0024]

[Table 1]

[0025]According to the following reaction formula, the de2-hydroxyphenyl-ized reaction was performed for the compound obtained in the reference example example 1. That is, this compound (0.4mmol) was first dissolved in acetone (3 ml), and the methyl iodide (1 ml) was added at the room temperature. After 8-hour stirring, the saturated ammonium chloride solution was added under ice-cooling, the reaction was suspended, the methylene chloride extracted, decompression distilling off after desiccation and of the solvent was carried out with anhydrous sodium sulfate, and the methyl ether object was acquired. This was dissolved in acetonitrile (3 ml) and the solution (1 ml) of cerium nitrate (IV) ammonium (1.2mmol) was added under ice-cooling. 1 hour afterward, reaction mixture was diluted with water and ethyl acetate extracted. 5% sodium carbonate solution, 10% sodium sulfite solution, 5% sodium carbonate solution, and a saturation salt solution washed the organic layer one by one, and decompression distilling off of the solvent was carried out after desiccation with anhydrous sodium sulfate. beta-aminoester derivative compound which refines with silica gel column chromatography and has an amino group of isolation was obtained (67% of yield).

[0026]

[Formula 6]

[0027]

[Effect of the Invention]According to a new dissymmetry zirconium catalyst, the invention of this application advances an imino aldol reaction catalytically, and gives optical activity beta-aminoester with high chemicals yield and a high asymmetric yield as it was explained in detail above. It is useful also as an asymmetric catalyst of not only an imino aldol reaction but a similar reaction.

(19) 日本国特許庁 (JP)

## (12) 公開特許公報 (A)

(11) 特許出願公開番号

特開平11-33407

(43) 公開日 平成11年(1999) 2月9日

(51) IntCl. <sup>6</sup>	識別記号	F I	
B 0 1 J 31/22		B 0 1 J 31/22	Z
C 0 7 B 53/00		C 0 7 B 53/00	B
C 0 7 C 227/12		C 0 7 C 227/12	
229/34		229/34	
327/22		327/22	

審査請求 有 請求項の数13 O L (全 8 頁) 最終頁に続く

(21) 出願番号 特願平9-197589  
 (22) 出願日 平成9年(1997) 7月23日

特許法第30条第1項適用申請有り 平成9年3月12日  
 社団法人日本化学会発行の「日本化学会第72春季年会  
 1997年講演予稿集 I」に発表

(71) 出願人 396020800  
 科学技術振興事業団  
 埼玉県川口市本町4丁目1番8号  
 (72) 発明者 小林 修  
 東京都千代田区築港町1-6-6-702  
 (74) 代理人 弁理士 西澤 利夫

(54) 【発明の名称】 不斉ジルコニウム触媒

(57) 【要約】

【課題】 不斉イミノアルドール反応等の不斉有機合成を高い反応性と選択で触媒的に行うことを可能とする。  
 【解決手段】 ジルコニウム (IV) を触媒の活性中心原子とし、2分子の光学活性なピナフル基と酸素原子を介して結合している構造の不斉ジルコニウム触媒を提供する。